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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/436,892 11/09/99 MEDFORD

R 04676.105045

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HM22/1106

EXAMINER

GABEL, G

ART UNIT

PAPER NUMBER

1641

DATE MAILED:

11/06/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

**Office Action Summary**

Application No.

09/436,892

Applicant(s)

MEDFORD ET AL.

Examiner

Gailene R. Gabel

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 20 August 2001.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-36 is/are pending in the application.
- 4a) Of the above claim(s) 7, 8, 11-14 and 16-20 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-6, 9, 10, 15 and 21-36 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☒ Claim(s) 1-36 are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All   b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)                      4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)                      5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_                      6) ☐ Other: \_\_\_\_\_

## **DETAILED ACTION**

### ***Amendment Entry***

1. Applicant's amendment and response filed 8/20/01 is acknowledged and has been entered. Claims 1-2, 4-6, 9, 10, and 15 have been amended. Claims 21-36 have been added. Claims 1-36 are pending. Claims 1-6, 9-10, 15, and 21-36 are under examination.

### ***Abstract***

2. The abstract of the disclosure is objected to because the content as written is unclear and indecipherable. Correction is required. See MPEP § 608.01(b).

Applicant's amendment filed 5/7/01 was not entered in the application for reason of record. Specifically, the abstract was not submitted on a separate sheet of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

### ***Information Disclosure Statement***

3. The Office acknowledges receipt of 72.01439 which Applicant discloses as most representative of the French Patent for Examiner's consideration but no Information Disclosure Statement (PTO-1449) was filed therewith. Further, Applicant points to page 7, lines 28-33 for statement of relevancy on references AQ-AV. However, no relevancy statement relating to AQ-AV appears to be noted in the specification. Please clarify.

**Rejection Maintained**

**Claim Rejections - 35 USC § 112**

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-6, 9-10, 15, as amended, and new claims 21-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- A) Independent claim 1 with dependent claims 2-5 and 21-22;
- B) Independent claim 6 with dependent claims 10, 23-30 and 33-34;
- C) Independent claim 9;
- D) Independent claim 15 with dependent claims 31-32 and 35-36.

Claim 1 is incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. Specifically, claim 1 fails to positively and distinctly define that the compound binds cholesterol-containing low - density lipoprotein, from here on CC-LDL, so as to obtain and isolate CC-LDL from the host.

Claim 1, step c) is indefinite in reciting, " the compound has bound to the CC-LDL" because it implies but does not distinctly define that the compounds binds CC-LDL.

Claim 1, step d) lacks antecedent support in reciting, "the LDL receptor".

Claim 4 lacks antecedent support in reciting, "the binding".

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Claim 4 is ambiguous in reciting, "the binding of the compound to the complex" because in claim 1, step c), the compound binds CC-LDL to form the complex. Therefore, claim 4 is unclear as to what "complex" Applicant intends for the compound to bind.

Claim 5 lacks antecedent support in reciting, "the binding".

Claim 5 is ambiguous in reciting, "the binding of the compound to the complex" because in claim 1, step c), the compound binds CC-LDL to form the complex. Therefore, claim 5 is unclear as to what "complex" Applicant intends for the compound to bind.

Claim 6 is incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. Specifically, claim 6 fails to positively and distinctly define that the compound binds low-density lipoprotein, from here on LDL, so as to form a complex.

Claim 6, step ii) is indefinite in reciting, "the compound and the LDL form a complex" because it implies but does not distinctly define that the compounds binds to the LDL.

Claim 6, step iii) lacks antecedent support in reciting, "the binding".

Claim 9, preamble is vague and indefinite in reciting, "therapeutically useful" because the phrase "therapeutically useful" is subjective and lacks a comparative basis for defining its metes and bounds.

Claim 9 is incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. Specifically, claim 9 fails to positively and distinctly define that the compound binds LDL in the mixture.

Claim 9 is ambiguous and incomplete for omitting essential structural and functional cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. Specifically, it is unclear, in the claimed sandwich assay, how a comparison step is effected in the absence of a detection step, i.e. label and correlation step.

Claim 9, step ii) lacks antecedent support in reciting, "the LDL receptor".

Claim 9, step iii) lacks clear antecedent support in reciting, "the amount of LDL captured by the assay". Specifically, claim 9 implies, but does not distinctly define, that a solid phase is bound to the second antibody, that the second antibody is a capture antibody.

Claim 9, step iv) is ambiguous in reciting, "the amount of LDL captured by the assay" because it is unclear what Applicant intends to encompass by the phrase "capture by the assay".

Claim 15 is incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. Specifically, claim 15 fails to positively and distinctly define that the compound binds CC-LDL in vivo, so as to obtain and isolate the resulting complex.

Claim 15, step c) lacks antecedent support in reciting, "the binding".

Claim 15, step c) lacks antecedent support in reciting, "the LDL hepatic receptor".

Claim 21 lacks antecedent support in reciting, "the lipoprotein receptor".

Claim 22 lacks antecedent support in reciting, "the low density lipoprotein hepatic receptor".

Claim 23 lacks antecedent support in reciting, "the cholesterol-containing lipoprotein".

Claim 25 lacks clear antecedent support in reciting, "the binding of the compound".

Claim 25 is ambiguous in reciting, "the binding of the compound to the complex" because in claim 6, step ii), the compound (binds) forms a complex with LDL. Therefore, claim 25 is unclear as to what "complex" Applicant intends for the compound to bind.

Claim 26 lacks clear antecedent support in reciting, "the binding of the compound".

Claim 26 is ambiguous in reciting, "the binding of the compound to the complex" because in claim 6, step ii), the compound (binds) forms a complex with LDL. Therefore, claim 26 is unclear as to what "complex" Applicant intends for the compound to bind.

Claim 28 lacks antecedent support in reciting, "the LDL receptor".

Claim 28 lacks antecedent support in reciting, "the low density lipoprotein hepatic receptor".

Claim 29 lacks antecedent support in reciting, "the control".

Claim 30 lacks antecedent support in reciting, "the CC-LDL".

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Claim 31 lacks clear antecedent support in reciting, "the binding of the compound".

Claim 31 is ambiguous in reciting, "the binding of the compound to the complex" because in claim 15, step a), the compound (binds) forms a complex with cholesterol-containing lipoprotein. Therefore, claim 31 is unclear as to what "complex" Applicant intends for the compound to bind.

Claim 32 lacks clear antecedent support in reciting, "the binding of the compound".

Claim 32 is ambiguous in reciting, "the binding of the compound to the complex" because in claim 15, step a), the compound (binds) forms a complex with cholesterol-containing lipoprotein. Therefore, claim 32 is unclear as to what "complex" Applicant intends for the compound to bind.

Claim 33 lacks antecedent support in reciting, "the apolipoprotein".

Claim 34 lacks antecedent support in reciting, "the low density lipoprotein receptor".

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application



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by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

5. Claims 1-3, 6, 21-22, 23-24 and 28 are rejected under 35 U.S.C. 102(b) as being inherently anticipated by MAO et al. (WO 95/15760).

To reiterate, Mao et al. disclose a method for assessing whether a compound binds to a lipoprotein in a manner which lowers plasma cholesterol by administering or mixing the compound/drug with a cholesterol-containing lipoprotein in vivo, incubating the resulting complex, and determining whether the binding of the compound to low density lipoprotein (LDL) causes an inherently change to the conformation of lipoprotein, apoB-100; thus enhancing its affinity to LDL receptor (see Abstract and page 2). Specifically, MAO et al. disclose administering certain 2,6-di-alkyl-4-silyl-phenols including those synthesized in pages 7-14 to lower cholesterol levels in patients with hypercholesterolemia. The compound can be administered orally, subcutaneously, intramuscularly, intravenously, etc. (see page 16). MAO et al. discuss classification of lipoproteins according to their density and function in page 2: chylomicrons transport dietary triglyceride and cholesterol to the adipose tissue and liver, VLDL deliver triglycerides from the liver to adipose and other tissues, and LDL transport cholesterol to peripheral tissues. Absent evidence to the contrary, the compound disclosed by Mao et al. would have inherently caused LDL to change in conformation so as to bind an LDL receptor to enhance clearance of cholesterol-containing LDL from peripheral tissues, i.e. plasma.

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6. Claims 1-3, 6, 21-22, 23-24 and 28 are rejected under 35 U.S.C. 102(b) as being inherently anticipated by OATES et al. (The New England Journal of Medicine, 1988).

Oates et al. teach a compound/drug (mevastatin or compactin and lovastatin) that inhibits HMG-CoA reductase and markedly lowers cholesterol and LDL levels in patients. Oates teach that in assessment studies (Bilheimer et al.), reductase inhibitors are administered to patients and found that they appear to increase receptor mediated clearance of LDL in the patients; thus qualifying as LDL clearance enhancing compounds (see page 25).

Lipoproteins are classified according to their density and function: chylomicrons transport dietary triglyceride and cholesterol to the adipose tissue and liver, VLDL deliver triglycerides from the liver to adipose and other tissues, and LDL transport cholesterol to peripheral tissues. Absent evidence to the contrary, the compound disclosed by Oates et al. would have inherently caused LDL to change in conformation so as to bind an LDL receptor to enhance clearance of cholesterol-containing LDL from peripheral tissues, i.e. plasma.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 4-5, 9-10, 15, 25-27, 29-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over MAO et al. (WO 95/15760) or OATES et al. (The New England Journal of Medicine, 1988) in view of KOREN et al. (US 6,107,045).

Mao et al. and Oates et al. have been discussed supra. Mao et al. and Koren et al. differ in failing to teach quantitating lipoproteins and apolipoproteins using sandwich immunoassay or agarose electrophoresis.

Koren et al. disclose quantifying immunoreactive concentrations of lipoprotein and apolipoprotein, including apoB-100 (LDL and VLDL) using sandwich immunoreactivity assays wherein antibodies specific to apoB-100 (known to be important in LDL receptor binding process) are immobilized into microwells as capture antibodies and labeled as secondary antibodies to capture and quantify the LDL concentration, respectively (see columns 11-12). Immunoreactive concentration of LDL is determined by ELISA or polyacrylamide gel electrophoresis (see columns 13, 18, and 20).

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One of ordinary skill in the art at the time of the instant invention would have been motivated to use the sandwich immunoassay or agarose electrophoresis such as disclosed by Koren to detect binding for the screening of compounds such as in the methods taught by Mao or Oates because Koren specifically disclosed that his assay provides antibodies specific for epitopes required for quantitation of LDL, VLDL, or apoB-100 for use in determining accurate antigenic levels in serum and plasma samples.

8. No claims are allowed.

9. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

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10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday-Thursday from 6:30 AM - 4:00 PM and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (703) 308-3399. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



Gailene R. Gabel  
November 5, 2001  
Art Unit 1641



LONG V. LE  
SUPERVISORY PATENT EXAMINER  
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11/05/01